

Review

How the ventral pathway got lost – And what its recovery might mean

Cornelius Weiller*, Tobias Bormann, Dorothee Saur, Mariachristina Musso¹, Michel Rijntjes¹

Dept. of Neurology, University of Freiburg, Germany

ARTICLE INFO

Article history:

Accepted 23 January 2011

Available online 22 March 2011

Keywords:

Aphasia

Wernicke

Dual loop model

ABSTRACT

Textbooks dealing with the anatomical representation of language in the human brain display two language-related zones, Broca's area and Wernicke's area, connected by a single dorsal fiber tract, the arcuate fascicle. This classical model is incomplete. Modern imaging techniques have identified a second long association tract between the temporal and prefrontal language zones, taking a ventral course along the extreme capsule. This newly identified ventral tract connects brain regions needed for language comprehension, while the well-known arcuate fascicle is used for "sensorimotor mapping" during speech production. More than 130 years ago, Carl Wernicke already described a ventral connection for language, almost identical to the present results, but during scientific debate in the following decades either its function or its existence were rejected. This article tells the story of how this knowledge was lost and how the ventral connection, and in consequence the dual system, fits into current hypotheses and how language relates to other systems.

© 2011 Elsevier Inc. All rights reserved.

1. Introduction

There is a striking contrast between our textbook perception of the anatomy of language processing and current neurobiological theories. Almost all textbooks about language refer to an iconic diagram with an anterior "language center" in the inferior frontal region, labeled Broca's area, commonly related to speech production, and a posterior temporal region, Wernicke's area, related to speech comprehension. These are connected through a single fiber system above the level of the ventricles, the arcuate fascicle, along which language information is transferred (Geschwind, 1972). However, in an analogy to the visual system with a dorsal "where" and a ventral "what" stream (Mishkin, Ungerleider, & Macko, 1983), current models assume a dual system to connect temporal and frontal cortices for language processing (Hickok & Poeppel, 2007; Kaas & Hackett, 1999; Parker et al., 2005; Rauschecker, 1998; Scott, Blank, Rosen, & Wise, 2000; Scott & Johnsrude, 2003; Wise, 2003) with "two broad processing streams, a ventral stream, which is involved in mapping sound onto meaning, and a dorsal stream, which is involved in mapping sound onto articulatory based representations" (Hickok & Poeppel, 2004). New approaches combining the most advanced in vivo imaging techniques for the human brain have now been able to verify this dual stream model functionally and anatomically (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Frey, Campbell, Pike, &

Petrides, 2008; Makris et al., 1999; Parker et al., 2005; Saur et al., 2008). The well-known arcuate fascicle connects regions in superior temporal gyrus and premotor cortex (BA 6/44), active during repetition of pseudo-words. A clearly separate ventral tract connects brain regions activated during sentence comprehension, in the middle temporal gyrus (and fusiform gyrus) and the ventro-lateral prefrontal cortex. It runs below the sylvian fissure along the inferior part of the claustrum, through the extreme capsule, behind the insular cortex (Saur et al., 2008).

This is exactly the region where Wernicke located the main connection between the frontal and the temporal lobe for language processing (Wernicke, 1874). However, consecutive errors, misinterpretations and misconceptions in the scientific community led to oblivion of knowledge about this obviously crucial ventral pathway for more than 130 years.

Meynert was the first to ascribe a language function to a formation of the claustrum, the insula, as well as the ascending acoustic fibers in the external and extreme capsule by reporting three cases with disturbed auditory comprehension, fluent speech and paraphasia with lesions of the temporal lobe and the insula (Meynert, 1866). A few years later, Bastian (1869) and Schmidt (1871) acknowledged the clinical syndrome of sensory aphasia, consisting of impaired comprehension with intact hearing, but without providing an anatomical location.

Carl Wernicke was only 26 years old, a doctorate student of Meynert in Vienna, when he presented a "physiological model on an anatomical basis", based on 10 patients, with post mortem findings in four of them (Wernicke, 1874) (Fig. 1). In addition to Broca's speech production center, "the center for images of movement for sound production in the first frontal convolution (b)", he proposed

* Corresponding author. Address: Neurologische Universitätsklinik Freiburg, Breisacherstr. 64, D-79106 Freiburg, Germany. Fax: +49 761 270 5310.

E-mail address: Cornelius.weiller@uniklinik-freiburg.de (C. Weiller).

¹ Shared last authorship.

“a sensory language center (a_1), containing the storage of sound images of speech in the first temporal convolution”. The interaction between both regions needed a connection “ $a_1 b$ ”, which Wernicke positioned in the deep white matter behind the insula: “The psychic reflex loop is mediated through the converging fibrae propriae in the insula” (Wernicke, 1874). He used this model to predict distinct clinical syndromes from lesions of either a “center” or of a connection between these centers. A lesion of a_1 would result in sensory aphasia (later termed “Wernicke-aphasia”; note that in contrast to later perception, for Wernicke sensory aphasia was “an acoustic defect” while meaning was only indirectly affected) (Wernicke, 1906). Lesion of b would result in Broca’s-aphasia. For lesions of the connection “ $a_1 b$ ” Wernicke introduced the term “Leitungsaphasie” (Wernicke, 1874) translated as “conduction aphasia” (Wernicke, 1903). It was characterized by the production of paraphasia along with attempts to correct, as well as difficulties in writing. In the current neuropsychological literature on conduction aphasia, phonemic paraphasia and attempts to correct (“conduite d’approche”) are present in spontaneous speech along with a significant impairment of word repetition, whereas comprehension is by and large preserved (Kohn, 1992). However, Wernicke did not mention repetition impairment as a major problem in conduction aphasia and his two cases with conduction aphasia (case 3 + 4, Beckmann and Kunschkel) (Wernicke, 1874)

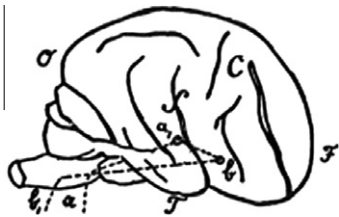


Fig. 1a. Wernicke’s “physiological model on an anatomical basis” of language processing from 1874 (Wernicke, 1874), displaying two central brain regions (a_1) “the sensory language center”, containing the “sound images of speech” and (b) “the motor language center”, which contains the images of movements for sound production. Both centers are connected by a single connection ($a_1 b$), the “fibrae propriae” in the depth of the insula. a = entrance of the *N. acusticus* in the brain stem; b_1 = exit of centrifugal pathways in the brain stem nuclei serving articulation. Note that this diagram shows the right hemisphere of a brain of a monkey. In the original figure “ a_1 ” was written as “ a ” but in the text constantly mentioned as “ a_1 ”.

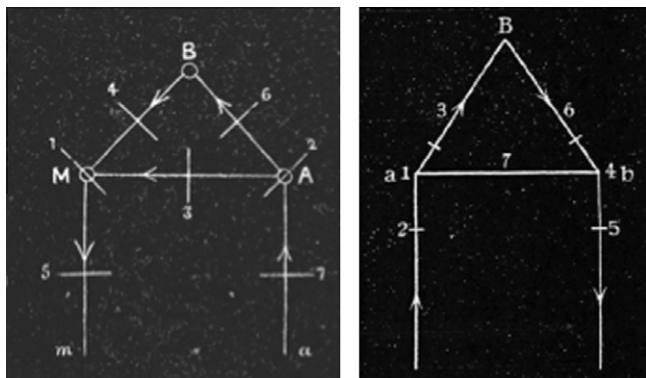


Fig. 1b. The iconic “house” diagram of Lichtheim from 1885 (Lichtheim, 1885) on the left and according to Wernicke’s text from 1906 (Wernicke, 1906) on the right (numbers refer to aphasic syndromes). Note that Lichtheim displays a left hemisphere and Wernicke a right hemisphere view. Lichtheim had introduced a “center for object concepts” (B), which is not a single localized center. As the representation of concepts is distributed around the cortex, processing streams along the concept center, the “indirect” route (a B b) are not uniquely specified in anatomical terms but referred to as transcortical connections.

were not characterized by a prominent deficit in repetition. Thus, Wernicke postulated a ventrally located connection behind the insular cortex to integrate both language centers in the temporal and frontal lobes. He introduced the term conduction aphasia (CA), which he assumed to be caused by a lesion of the pathway. In contrast to today’s taxonomy, however, CA was not characterized by a repetition deficit.

2. The loss of the ventral pathway

In the following decades, the postulate of a ventral connection was rejected. The main reason was the concept of conduction aphasia (CA). The connotation of CA with repetition is often related to the name of Lichtheim, which is not entirely correct. With Lichtheim’s introduction of a “concept center” (“B”) (Fig. 1) (Lichtheim, 1885), the path “(A) B M” had become the route for volitional speech. In contrast, “AM”, which corresponds to the “direct” route “ $a_1 b$ ” in Wernicke’s notation, merely served non-volitional speech (considered as a “reflex”), i.e. repetition. Although repetition should be impaired after disruption of AM (resp. “ $a_1 b$ ”), Lichtheim did not see impairment of repetition as specific for CA as an alternative route via volitional speech was available (Lichtheim, 1885). The characteristic feature of CA would be paraphasia in all tasks requiring speech production as proposed by Wernicke (De Bleser, Cubelli, & Luzzatti, 1993; Wernicke, 1874).

In 1891 Sigmund Freud, at that time neuropathologist in Vienna, who had also been a student of Meynert from 1882 until 1885, criticized the model that Wernicke had developed (Freud, 1891). The interaction between “sound perception” in a_1 and “sound production” in b would be crucial in repetition: “Repetition is the task of this tract. Therefore, the consequence of its disruption should be the inability to repeat with intact spontaneous speech and comprehension. It is obvious to everybody that such a dissociation of language abilities had not been observed and has no likelihood ever to be expected” (Freud, 1891). As there could be no such exclusive loss of repetition, Freud concluded that “the tract that is used for speaking is identical with the one along which repetition is performed” (Freud, 1891). Consequentially, conduction aphasia could not exist and lesions of the insula should cause a different (still to be explored) type of speech disorder. Still, the idea persisted that a lesion in the connection between the two language centers would cause a deficit in repetition. With Heilbrunner (1908) it became the accepted doctrine. Kleist even introduced the term repetition-aphasia (Kleist, 1934).

The second reason was that the ventral connection was eclipsed by another. The discussion about CA began at the same time when an anatomical fight had erupted between those backing a ventral connection and those preferring the arcuate fascicle for connecting the posterior part of the temporal lobe with the (inferior) frontal lobe. A ventral tract, described by Trolard (1906) and displayed in atlases as the frozen sections of Ludwig and Klingler (1956) aligns within a relatively narrow complex around the inferior part of the claustrum, running through the extreme or the external capsule below the level of the basal ganglia and seems to coincide with Wernicke’s prediction. However, the arcuate fascicle, originally described by Reil (1809) and in detail by Burdach (1826), was promoted by many highly influential researchers: von Monakow (1885) and Charcot (as cited by Bernard, 1885) rejected any other direct connections between the temporal and the frontal lobe. In 1908, (2 years after Wernicke’s publication from 1906, defending his findings from 1874) several meetings took place in Paris to determine the succession of Charcot as head of Neurology in the Salpêtrière. One of the candidates was Marie, who stated that he did not know, whether or not the insula, the external capsula or the claustrum played any role in aphasia. The other one, Dejerine,

cited one case of a patient having an insular lesion without aphasia, and flatly denied it (Lecours, Chain, Poncet, & Nespoulos, 1992).

The third reason was that after the initial euphoria about localizing brain functions, the proponents of equipotentiality got the upper hand again. For example, Freud was reluctant to localize speech functions in the brain at all (Freud, 1891). Instead, he believed that language would be the result of processes distributed across the entire cortex. For Freud there were only associations and no centers, and all types of aphasia would be caused by disruption of fibers. Aphasia due to a lesion of a “center” would be “nothing else but aphasia through lesions of association tracts, which converge, diverge or pass through this node, which we use to call center” (Freud, 1891). Freud’s view was *à la mode*, as with the turn of the new century the pendulum swung back to holism, and “diagram makers” (Head, 1926) went out of style. With the increasing influence of Kraepelin (1901), neuro-psychiatry took another route towards “empirical psychopathology” and “holistic psychology” (Geschwind, 1965), almost without relation to brain anatomy.

Finally Geschwind, recognizing Wernicke as the first one to propose a disconnection syndrome, picked up the concept of conduction aphasia again. Geschwind accepted and promoted repetition failure as the predominant feature of conduction aphasia: “The special impairment of repetition is adequately explained by the disturbance of the link from Wernicke’s to Broca’s area” (Geschwind, 1965). Geschwind referred to von Monakow’s emphasis on the importance of the arcuate fascicle and concluded that conduction aphasia should result from a lesion of this fiber tract. Geschwind’s inclination towards the arcuate fascicle may have been influenced by the importance he attributed to the angular and supramarginal gyrus in the parietal cortex as multimodal integration areas needed for speech development and for comprehension: “the function of Wernicke’s area implies the existence of extensive connexions to the angular gyrus region” (Geschwind, 1965). He backs his view by citing the English publication of 1908 (Wernicke, 1908), in which Wernicke allegedly had given up the idea that lesions of the insula would cause conduction aphasia: “He (Wernicke) stated here that the autopsy findings had not confirmed his view that conduction aphasia was the result of lesions in the insula.” (Geschwind, 1965)

3. Back to Wernicke

In the many reports after Wernicke’s first publication, hardly any patient was found with conduction aphasia with repetition problems and insular lesions (Pershing, 1900). In consequence, in his later papers, Wernicke discussed Lichtheim’s model and responded to his critics by revising his theory about conduction aphasia (Wernicke, 1886, 1906). Wernicke admitted that his original explanation from 1874 for the clinical syndrome of CA with paraphasia due to a lesion to the direct tract “a₁ b” was incomplete and added features to this syndrome, including “loosening of the word concept” and the inability to repeat, which he limited to the repetition of meaningless words.

Wernicke introduced the term “word concept” (“Wortbegriff”) (Wernicke, 1906). This would be constituted out of the respective sensory and motor representations in a₁ and b, as well as its connection “a₁ b”: “The possession of both of these memory pictures, intimately combined for each word, is what the French authors have designated as “internal speech”. For this reason I proposed the designation “word concept”, recognizing the acquirements of word concepts to be the most important process in learning to speak.” (Wernicke, 1903) “Word concept” or “inner speech” would be related to “a₁ b”, as Wernicke deduced from patient observation with transcortical aphasia, in which “a₁ B” and “B

b” are destroyed but “a₁ b” and in consequence “inner speech” remains intact (Wernicke, 1906).

Already in his first treatise, Wernicke saw “repetition as the generic accomplishment of the tract aa₁ bb₁”. “The main task of the child that learns to speak is the imitation of the heard word; only later the child is able to bind this word with a defined concept, long after the word has become a vast asset” (Wernicke, 1874). But later on words would be spoken via the semantic route: “Soon after we have learned to speak a word, we lose the intention only to reproduce sounds and plan to utter a meaning” (Wernicke, 1874). “We have to assume that (then) the majority of speech impulses reach the word concepts from the remaining cerebral cortex” (Wernicke, 1906). He added the distinction of repetition of pseudo-words versus words. In CA, repetition of meaningful material should be possible via the indirect semantic route. However, repetition of meaningless material should be impossible if “a₁ b” (or “AM”) is disrupted: “If the mere sound of a word is sufficient for its full understanding. . . and if words can be spontaneously spoken without the previous stimulation of the sound image (note: the two arguments imply an independence of both centers, a₁ and b in Fig. 1, an assumption, Wernicke did not share), then after interruption of the association tract between sensory and motor speech centers, it should still be possible to repeat at command words, which have a meaning.” “ evidentiary for the existence of this oldest tract should only be the (existence of) direct repetition, the so-called echolalia, automated and without behest. or (the ability) to repeat words, which are incomprehensible, as such from a completely unknown language. Should there be cases in which this particular form of repetition is impossible. . . Yet on the other hand the power of speech and its understanding would be retained. . . (and the cases would present with) with paraphasia and the ability to criticize the errors that have been made. (Then) I would consider the clinical requirements (for conduction aphasia through destruction of the tract “a₁ b”) to be sufficiently fulfilled” (Wernicke, 1906). He continues: “I cannot, however, refrain from emphasizing that the autopsy findings (for example, exclusive or predominant destruction of the insula) are not calculated to support the view of conduction aphasia postulated by me” (Wernicke, 1903, 1906). It was this last sentence, which Geschwind referred to, when he stated that Wernicke “came to accept. . . the view, that the lesion for it (i.e. conduction aphasia) lay in the arcuate fascicle” (Geschwind, 1967). However, when reading carefully Wernicke’s entire text from 1906 (the German text as well as the English text from 1908 were published after Wernicke’s death in 1905), it can be concluded, that Wernicke explicitly disagreed with von Monakow’s and Dejerine’s preference for the arcuate fascicle: “The importance of the insula for the function of speech. . . permits us to conclude that it is the objective point for the association tracts, and the area where the two centers of speech, and presumably also the different areas of the speech region, unite with each other. In fact the finer anatomy of the region of the insula permits no other explanation than that we are dealing with an actual association center.” (Wernicke, 1906)

Thus, both Geschwind and Wernicke were aware of more than one tract, potentially connecting the temporal and frontal language zones. Wernicke mentioned the “uncinate, which appears to unite by the shortest possible connection” and the arcuate fascicle, which he saw “not actually a special bundle, but a general system of association fibers, which must be considered in the anatomy of speech regions” (Wernicke, 1903). Still, what remained was a continuing bias in favor of the arcuate fascicle (Catani, Jones, & ffytche, 2005; Friederici, 2009; Rilling et al., 2008; Weiller, Musso, Rijntjes, & Saur, 2009).

Wernicke recognized the need to use two routes for normal language, the route from the concept center B to the images of movement for sound production, i.e. “B b” (Fig. 1) and the route “a₁ b”

for automated correction, which accompanies speech production: “during normal speech, it seems, the sound image of a word is unconsciously being innervated as well, exerting a constant correction on the sequence of the images of movement of speech” (Wernicke, 1874). Paraphasia would be the result of a lack of this correction: “a defect in a regulatory influence of the sound images of language on the act of speaking”... “the patient understands everything and can speak everything, however the selection of words is disturbed” (Wernicke, 1906). The sound image would still be intact but could not take appropriate influence on the selection of motor images. “Thus words are confounded, but correction is possible... consciously, and with focussed attention... as the sound of the spoken word is transported to the place of the sound images” (which are intact) (Wernicke, 1874). Wernicke recognized the ability to correct as the main difference to sensory aphasia with similar output problems: In sensory aphasia “the patient is unaware of the incorrect or correct use of words”. Whereas in conduction aphasia “another correction is obvious, in which, only seldom used during normal speech, the unaware mode is gradually substituted by a conscious, intentional mode... The attentive patient realizes that a spoken word was incorrect” (Wernicke, 1874).

4. Putting history in the context of contemporary neuroscience

The historical overview shows that the debate on single or dual processing streams underlying the generally accepted two routes model for normal language processing can be traced back to the 1870s and the intense debate between Wernicke, Lichtheim, Freud and Geschwind. History tells us how easy the mistake is made to promote a single, “unifying” pathway for language. This hinders the assumption of a dual loop system of the brain necessary for the development of such complex functions as language. Since two anatomical tract systems were known and different functions for the connection between Wernicke’s and Broca’s area had been attributed, it would have been possible from the beginning to reconcile these facts. On hindsight, it is somewhat surprising that this step was not taken.

Wernicke developed a central and very modern idea of language processing to its full extent. Note that he did not promote “comprehension” or “speech production” as segregated features of the brain but rather two basic mechanisms: “sensory–motor integration” – needed for language production and learning to speak (as well as repetition of meaningless words) – and integration of representations in the sensory and motor centers with non-linguistic conceptual representations – as a possible mechanism underlying comprehension.

In essence, language emerges through the interaction of two centers. This interaction is accomplished through two principal routes (Fig. 1). The route “a₁ b” is called the “direct route” by Wernicke. The term “direct” does not necessarily refer to a direct fronto-temporal anatomical connection (see below) but to a direct “functional” interaction between Wernicke’s (center of sound images) and Broca’s area (center for images of movement). The “indirect route” is indirect because it connects both centers through the “concepts”. This idea was generally accepted but the discussion was about the anatomical course of these routes. Wernicke’s postulated the existence of a ventral connection. However, he ascribed a function to it, sensorimotor integration, which today would be related rather to the dorsal connection along the arcuate fascicle. Meaning would be an accomplishment of the interaction of both Wernicke’s area in the temporal lobe and Broca’s area in the frontal lobe with representations of (non-linguistic) concepts distributed around the cortex along the indirect pathway. Lesioning of these connections should lead to transcortical aphasia. These connections were not anatomically specified and should consist of

multiple association tracts between the sensory or the motor language center and the projection fields concerned with the formation of a concept (Wernicke, 1906). We propose that the ventral tract along the insula through the extreme capsule constitutes the anatomical correlate for this interaction. Clearly, Wernicke was not as explicit as that. He did not really differentiate between word and sentence level and did not include parietal cortex, thalamus, the caudate nucleus and the right hemisphere.

Even if despite recent publications (Catani et al., 2005; Ross, 2010), two pathways for language may be more or less generally accepted by now (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009), important issues remain, concerning origin, course and endings of the pathways and moreover the exact function of the connection as well as the issue of exclusivity or dominance of one or the other tract in human evolution.

5. Solutions from anatomy

Recent anatomical studies resolve at least the anatomical issue in the historical debate. Evidence for a ventral connection as proposed by Wernicke comes foremost from axonal tracing experiments in monkeys, which individuated at least two ventral pathways connecting temporal with frontal areas: the extreme capsule and the uncinate fascicle. The extreme capsule connects superior temporal sulcus (e.g.; area TPO), superior temporal gyrus (T1a, paAlt, TAa, TS3), planum temporale, middle temporal region (TS2), inferiortemporal region (i.e. area TE) and rostral insula with the frontal lobe – primarily with area 45 (pars triangularis, F3t), frontal operculum (FO), area 47 (mostly from anterior middle region) and with a modest contingent of fibers terminating in area 44 and has projections to the dorsolateral cortex (9/46) and ventral area 10 (Petrides & Pandya, 1988, 2007, 2009; Schmahmann & Pandya, 2006). From the inferior parietal lobe, PG and PFG are connected with the superolateral temporal region via the middle longitudinal fasciculus (MDLF) (Seltzer & Pandya, 1984) and with fibers through the extreme capsule to the ventro-lateral prefrontal cortex (Berke, 1960). Thus, the fibers in the extreme capsule (which in part overlap with tracts called fasciculus occipito-frontalis inferior (Gloor, 1997), inferior occipital fascicle (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009) or inferior fronto-occipital fascicle (IFOF) (Catani, Howard, Pajevic, & Jones, 2002)) allow for integration of information between the temporal, the parietal and insular cortex with prefrontal cortices (Bucy & Klüver, 1955; Gloor, 1997).

Today, the dorsal tract system is generally subdivided in superior longitudinal fasciculi (SLF) and arcuate fasciculus (AF), in non-human primates connecting area PG (corresponding to the angular gyrus in humans), area PF (equivalent to human rostral supramarginal gyrus), PFG (corresponding to the caudal part of the supramarginal gyrus) and adjacent superior temporal sulcus with the homologs of Broca’s region in the frontal lobe (BA 44 and 45) and the surrounding dorsal and ventral areas 6 and 9/46 (Petrides & Pandya, 2009; Schmahmann & Pandya, 2006).

Tracking experiments in humans are based on diffusion tensor imaging, which currently lacks the resolution to establish the origins and precise terminations of the tracts, therefore they are less exact but in principle congruent with animal tracing data (Anwander et al., 2007; Catani et al., 2005; Croxson et al., 2005; Friederici, 2009; Makris & Pandya, 2009; Parker et al., 2005; Powell et al., 2006; Saur et al., 2008).

In humans, there is evidence for a dichotomy in dorsal routes with a “classical arcuate pathway connecting Broca’s and Wernicke’s area directly” as well as an “indirect pathway passing through inferior parietal cortex” (Catani et al., 2005). The effective course of the ventral routes is momentarily unclear. The fibers in the extreme capsule are interwoven with the claustrum and the

insular cortex, as already Wernicke pointed out (Wernicke, 1874, 1906). As far as Wernicke's texts are concerned, it remains an open question whether anatomically he saw the “direct route” “a₁ b” constituted by an uninterrupted tract, bypassing any gray matter (“the psychic reflex loop. . .”), or uses the insula as “an actual association center” (Wernicke, 1874, 1906). As pointed out above, even today this question is difficult to answer in humans with the available techniques. Also classical neuropsychological lesion studies do not differentiate lesions of gray matter from those of white matter. Exemplary, this may apply to the excellent study of Dronkers (1996). She found the “precentral gyrus of insula” as a critical region for apraxia of speech. However, from her work we cannot conclude whether the ventral tract or even the dorsal tract is affected as well. Tracking experiments in monkeys have shown a direct connection, which is confirmed by recent DTI work in humans for the language system (Frey et al., 2008; Saur et al., 2008) as well as in other domains (Umarova et al., 2010; Vry et al., 2009). These findings are in line with the opinion that the ventral loop may be defined by multiple parallel routes with direct connections as well as serial connections taking synapse in the insula or claustrum, each serving a specific interaction but reflecting a common processing denominator.

6. A dorsal stream for the integration of sensory percept and internal models

In his model, Wernicke predicted sensorimotor mapping as the task of the route “a₁ b”, which codes and maintains instances of speech sounds, and uses these sensory traces to guide the tuning of speech gestures so that the sounds are accurately reproduced. This connection would support the formation and recall of “word without comprehension” (Wernicke's “Wortbegriff” with sensory and motor components) as in repetition and, moreover, in learning to speak. Wernicke was the first to suggest that the auditory–motor interaction circuit plays the crucial function in speech development, even if he gave this connection the wrong anatomical connotation. However, the idea of a sensorimotor mapping route can be found again in motor theories of speech perception that assume a link between sensory input and motor speech systems (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967; Liberman & Mattingly, 1985). Houde and Jordan (1998) found that adults learn to adjust their production of a vowel to compensate for feedback alterations that change the vowel's perceived phonetic identity. However, the dorsal stream is not limited to “mapping sound onto articulation”, but rather serves to integrate and maintain the perceived auditory signals within context over temporal and spatial evolution (Belin & Zatorre, 2000; Rauschecker, 1995, 1998) or to integrate linguistic elements within working memory (Patel, 2007), even to process phrase-structure grammar (Friederici, Bahlmann, Heim, Schubotz, & Anwender, 2006). The dorsal stream is not limited to “where” or “how” functions, rather its role is more general, independent from the domain, the capacity to analyze the sequence of segments, either in time or in space, as well as fast on-line integration between sensory event information and “internal models or emulators” (Rauschecker & Scott, 2009). Spatial transformation as well as sensorimotor integration (Hickok & Poeppel, 2007) may be examples of adaptations used by forward models (predictors) and inverse models (controllers) (Rauschecker & Scott, 2009). It is not clarified as yet whether or not working memory predominantly uses the dorsal stream. But the frontal areas involved in working memory, as pars opercularis or precentral cortex, are mainly connected via the dorsal fiber system with parietal and temporal lobe (Paulesu, Frith, & Frackowiak, 1993; Wager & Smith, 2003). These tracts may be involved in short-term retention of the phonological input and lesions to the inferior pari-

etal areas in the left hemisphere usually cause verbal short-term memory impairments (Vallar, Di Betta, & Silveri, 1997).

The mechanism for “on-line” analysis of sequences may be seen as a function of the dorsal system in other domains as well. A dorsal network was recently described in the attentional network, where dorsal streams along the superior longitudinal fascicle/arcuate fascicle system connected the parietal and temporal lobe with the premotor cortices (BA 6, 44, 8) and interpreted to convey information needed for spatial stimulus orientation or processing of peri-personal space (Umarova et al., 2010). A similar finding seems to exist in the motor system. During simple, repetitive, externally cued active or passive movements, a dorsal route connects the parietal cortex with premotor areas for sensorimotor mapping, motor control based on internal predictive models and sensory feedback (Vry et al., 2009).

7. A ventral stream for meaning

Most authors would agree that the ventral stream, in analogy to the visual “what” stream, is involved in processing speech signals for comprehension (Hickok & Poeppel, 2004; Makris & Pandya, 2009; Saur et al., 2008). As connecting tracts in the ventral stream the uncinate fascicle and the extreme capsule are in discussion. For Hickok and Poeppel (2007), mapping sensory or phonological representations onto lexical conceptual representations is the task of the ventral stream and involves “multiple bilateral routes” including middle temporal gyrus, inferior temporal sulcus and anterior temporal lobe (ATL). The relevance of ATL converges from several neuroimaging studies (for review see Warren, Crinion, Lambon Ralph, & Wise, 2009) as well as from neuropsychological studies in patients suffering from semantic dementia (Hodges, Patterson, Oxbury, & Funnel, 1992; Patterson, Nestor, & Rogers, 2007; Lambon Ralph & Patterson, 2008). As the ATL is connected via the uncinate fascicle (UF), the UF has been proposed as the relevant ventral route for language processing (Catani & Mesulam, 2008; Duffau, 2008; Friederici, 2009; Grossman et al., 2004; Lu et al., 2002; Matsuo et al., 2008; Parker et al., 2005; Wise, 2003). However, the frontal terminations of the UF seem to be centered in the medial and orbital prefrontal cortex (Catani et al., 2002; Schmahmann & Pandya, 2006), which may suggest that the UF is a limbic association pathway (Schmahmann & Pandya, 2006) and its disturbance in patients with semantic dementia may be related to changes in empathy, disinhibition, personality or compulsive symptoms, rather than to linguistic features of patients with semantic dementia (Agosta et al., 2010). In cases with semantic dementia the temporal lobe is not only atrophic but there is also alteration to the ventral tracts in the extreme capsule projecting to the frontal lobe (Agosta et al., 2010). Nevertheless, emotions play a major role in language, and it currently remains unclear whether “the semantic ventral stream might be constituted by at least two parallel pathways” (Duffau et al., 2009). An argument in favor of the extreme capsule comes from intraoperative deep stimulation, which interrupts language when the extreme capsule is stimulated but not when the UF is stimulated (Duffau et al., 2009). Moreover, in primates the anterior temporal lobe is connected to ventro-lateral prefrontal cortex via the extreme capsule (Petrides & Pandya, 2009).

Our previous study in humans found the extreme capsule as the site of the most likely course of fibers connecting the regions in the temporal and frontal lobes, activated during comprehension (Saur et al., 2008). Furthermore, regions related to semantic tasks in imaging experiments comprise not only the anterior temporal lobe but also STS (area TPO), STG (T1a, Taa, TS3), middle and inferior temporal regions (Vigneau et al., 2006), which in primates are connected with the inferior frontal gyrus regions (BA 45 and 47) by a ventral tract through the extreme capsule (Makris & Pandya, 2009;

Petrides & Pandya, 1988; Schmahmann & Pandya, 2006). In Hickok and Poeppel's model, the frontal lobe ending of the ventral stream has not exactly been determined and Broca's area is described only in context of the dorsal stream (Hickok & Poeppel, 2007). However, the inferior frontal gyrus is a heterogeneous area, with pars opercularis (area 44) connected mainly via the dorsal stream, while pars triangularis (area 45) as well as area 47 are mainly connected via the ventral stream (Petrides & Pandya, 2007, 2009). Although the involvement of the inferior frontal region in semantic processes at word level is less clear and has been disputed (Bookheimer, 2002), pars triangularis (BA 45) and pars orbitalis (BA 47) have been associated with the selection of relevant features of semantic knowledge from a set of competing alternatives (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Neuropsychological evidence as well suggests that this region is involved in control of semantic processing (Sharp et al., 2010).

The fronto-temporal interaction along the extreme or external capsule embraces the insula and the claustrum, anatomical structures with projections to almost all cortical regions (Edelstein & Denaro, 2004; Mathur, Caprioli, & Deutch, 2009). The role of the anterior Insula in language continues to be discussed. This region plays a specific role in the "speech initiation loop" (Dronkers, 1996) albeit the most dorsal part of it. Other authors postulate a pivotal function of the anterior insula in the integration of auditory information with other associative functions (Barmiou, Musiek, & Luxon, 2003) or in the temporal processing to prepare some initial categorization or grouping (Barmiou et al., 2006). The claustrum has been highlighted as a central converging cognitive structure important for consciousness by binding sensory input both within and across sensory modalities to generate conscious percepts (Crick & Koch, 2005).

Another region where relevance for semantic is in discussion since Geschwind's times is the angular gyrus (Vigneau et al., 2006). As a multimodal association cortex directly connected to visual, somatosensory and auditory association cortex (Geschwind, 1965) it serves as an interface between modalities and has been suggested to map perceptual input to distributed semantic knowledge (Binder, 2002). An alternative proposal is that the angular gyrus is part of a fronto-parietal network engaged in top-down-control of semantic processing in other regions (Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Sharp et al., 2010). Recent studies demonstrated that increasing functional connectivity between angular gyrus and prefrontal cortex (BA 47), which are directly connected only by fibers through the EmC, facilitates speech comprehension when the clarity of speech is reduced (Obleser, Wise, Alex Dresner, & Scott, 2007) or during increasing semantic complexity (Sharp et al., 2010). Thus the parietal cortex may not only be part of the dorsal system for verbal working memory but also involved in top-down-control of semantic processing in the temporal lobe, as well as in integration with prefrontal cortex for meaning along the ventral system. Note, however, that regions may support different functions, which are not mutually exclusive.

A ventral stream through the extreme capsule seems to play an important and similar functional role in other domains as well. In the attentional system, a ventral tract, connecting the parietal and temporal lobe with the anterior insula and ventro-lateral prefrontal cortex, was interpreted as being critical for the integration of conscious perception of space for an intended action and for the correct estimation of the relevance of stimuli to the self (Umarova et al., 2010). Similarly in the motor system, areas in posterior parietal and prefrontal cortices involved in imagery of movements are connected via the ventral route, putting the ventral tract in relation to symbolic acts and cognition (Vry et al., 2009). There is no reason to suppose that the organization in the acoustic language system is organized differently from other modalities.

8. An equivalent dual loop system, rather than exclusiveness or dominance

Clearly, the division in two routes is artificial, only found in experimental settings. Recent studies have highlighted the fact that semantic-conceptual and phonological segmental information interact closely. In patients with progressive semantic impairment, the repetition of word lists is defective, specifically for those words, which the patients fail to comprehend (McCarthy & Warrington, 1990; Patterson, Graham, & Hodges, 1994). A similar observation has been made for non-words (Jefferies, Bateman, & Lambon Ralph, 2005). Thus, even a non-word repetition task seems to involve semantic processing. This may explain the involvement of the ventral stream in non-word repetition (Saur et al., 2008). Close interaction is especially needed in sentence processing. There are different models of sentence processing, some assume early interaction of syntactic, lexical, semantic and pragmatic constraints (e.g., Altmann & Steedman, 1988; MacDonald, Pearlmutter, & Seidenberg, 1994; Marslen-Wilson & Tyler, 1980), while others assume late interaction (Frazier, 1987). However, all sources of information are eventually needed to understand the meaning of a sentence. Therefore, close interaction of the two pathways during sentence processing is expected.

Indeed, most imaging studies on real or artificial grammar processing (Bornkessel, Zysset, Friederici, von Cramon, & Schlesewsky, 2005; Caplan et al., 2002; Fiebach, Schlesewsky, Lohmann, von Cramon, & Friederici, 2005; Musso et al., 2003; Stromswold, Caplan, Alpert, & Rauch, 1996; Tettamanti & Weniger, 2006) show involvement not only of the heterogeneous inferior frontal gyrus but also of the insula and anterior superior temporal gyrus – probably relating to the ventral stream – as well as pre-SMA, supramarginal gyrus, inferior parietal lobe and posterior superior and middle temporal gyrus – more generally part of the dorsal stream. And indeed, Friederici (2009) and Friederici et al. (2006, 2008) demonstrated that processing phrase-structure grammar, which many linguistic theories agree to be characteristic for human language, involves both streams: a ventral interaction between frontal operculum and anterior STG and a dorsal one between pars opercularis and STG. The ventral stream is involved in processing phrase structure as well as finite state grammar. Thus, it seems that the "what" stream in syntax may be related to the identification of serial as well as long-distance syntactic relations of the perceived elements.

The dorsal stream seems to be used only for more complex grammar (Friederici, 2009). Friederici (2009) and Friederici et al. (2006, 2008) deny that this involvement results from working memory processing, as this mainly relates to activation not of the pars opercularis but of the left inferior frontal sulcus (Makuuchi, Bahlmann, Anwander, & Friederici, 2009). Rather, it is explained as an "effect of structural complexity" (Friederici, 2009). However, several others studies demonstrate that violation of serial and local dependencies in other artificial grammar experiments (Forkstam & Petersson, 2005), in pseudo-words sentences (Moro et al., 2001; Tettamanti et al., 2002) or in mathematical strings (Friedrich & Friederici, 2009) also involves left pars opercularis and parietal regions, rather than frontal operculum. It has alternatively been suggested that pars opercularis (BA44) and the dorsal stream emanating from it may play a role in "the linearization of hierarchical structure" (Bornkessel et al., 2005) or in "syntactic unification" (Forkstam & Petersson, 2005; Hagoort, 2005).

Therefore, in syntax as well as in speech production, the dorsal stream may serve the precise and rapid analysis of serial sequences. It detects and corrects ("calibrating") irregularities by relaying the timing of their occurrence to internal moulds or blueprints which are extracted and memorized in lifetime ("self monitoring" (Levelt, 1999)), as in verbal working memory. Syntactical violation is recognized through a ventral stream, which may

rapidly identify the syntactical relations within the acoustic elements, and a dorsal stream, which seems to be pivotally engaged when neural resources are necessary to integrate each single event within the context of sequential information that is structured according to internal abstract regularities.

In summary, rather than perpetuating the discussion around the question whether the arcuate fascicle (Catani et al., 2005; Glasser & Rilling, 2008; Ross, 2010) or rather a ventral tract (Makris & Pandya, 2009) would be more important for language, we advocate the notion that language needs a flexible and well interacting dual system, especially in sentence processing. For most functions, both streams are not mutually exclusive but rather work in parallel (Makris & Pandya, 2009; Rauschecker & Scott, 2009), constituting a loop which has to be passed at least once. This may explain the parallel or repetitive activation of frontal and temporal regions detected with high temporal resolution (Salmelin, Hari, Lounasmaa, & Sams, 1994).

A dual stream system has implications for the understanding of aphasic syndromes and recovery from aphasia. A bilateral, left-lateralised, parallel processing system with both a ventral and dorsal connection between temporal and frontal language zones gives ample options for compensatory processes after focal lesions resulting in a variety of active combinations of connections between cortical regions, which differ in a quantitative rather than an absolute manner. This assumption makes the complexity and fuzzy link of aphasic syndromes to focal lesions more understandable.

9. Levels and models

By accepting Lichtheim's introduction of conceptual representations independent of linguistic representations, Wernicke basically adopted a differentiation, which has by and large been maintained until now. Yet it can be found in his 1874 treatise where he notes that: "thinking and speaking are two independent processes, which even may inhibit each other" (Wernicke, 1874).

The distinction between phonological representations and non-linguistic representations of conceptual knowledge has been incorporated in most modern as well as historical models of language processing. The linguistic representations would correspond to Wernicke's "Wortbegriff". Both Kleist in an early, relatively neglected paper (Kleist, 1905) as well as Goldstein proposed the existence of an undifferentiated language area (Goldstein's "zentrales Sprachfeld" (Goldstein, 1927)). Note, however, that this area was not supposed to correspond to distinct cortical regions. Kleist had been influenced by Freud who in 1891 had described three levels of representation. The first level comprises a representation of the "Wortvorstellung" ('word-images'). Lesions at this level would cause "verbal aphasia", affecting the associations between the elements of the word images themselves.

A different, non-linguistic level of representation would be the complete set of associations (e.g. visual, somatosensory) connected with an object ("Objektvorstellung"). A lesion at this level would cause "agnostic aphasia" (the term "agnosia" was coined by Freud here, its first use in neurological literature (Freud, 1891)). At an intermediate level, Freud assumed associations between words and objects. A lesion at this level would lead to "asymbolic aphasia", in which the "word images" are unable to make the proper associations with representations associated with the word. This together with the first level would constitute the language system proper.

This points to a central issue, the question of how mapping is achieved between the conceptual and linguistic levels. As Jackendoff (2009) puts it: "Language is essentially a mapping between sound and 'propositional' or 'conceptual thought'." This idea of a functional overlap is also present in Vygotsky's idea of speech and thought as two overlapping circles (Vygotski, 1934) (Fig. 2). In

their overlapping parts, thought and speech coincide to produce what is called verbal thought or inner speech, depending on the point of view. Within this overlapping part, language represents the connection between speech and thought, as well as being its product. Through inner speech, however, language also provides a "scaffolding that makes possible certain varieties of reasoning more complex than are available to non-linguistic organisms" (Jackendoff, 1997).

In modern cognitive models of word processing, mapping is achieved through different intermediaries. In Levelt's model (Levelt, 1999), two levels of representations mediate between conceptual knowledge and a word's phonological content, lexical concepts and lemmas. Within an interactive model, Dell, Martin, and Schwartz (2007) assume a single level of lemmas to mediate between semantic features and phonological segments. Both of these cognitive models are so-called localist models. In the context of parallel, distributed neural network-type models (e.g., Lambon Ralph, 1998; Lambon Ralph, Sage, & Roberts, 2000), no localist representations are assumed for individual lexical entries. Still, for computational reasons so called 'hidden units' have to be incorporated to ensure mapping of meaning and sound.

Current models of word processing also provide a more detailed framework for repetition via meaning and via sound-to-phoneme mapping, comparable to Wernicke's ideas. Most cognitive models have argued for two or even three routes for repetition, some within the context of an interactive activation model (e.g., Dell et al., 2007; Hanley, Dell, Kay, & Baron, 2004) and others in the context of Morton's Logogen model (Morton, 1980).

Can the dual loop system be related to these cognitive models of language processing? Tentatively, the dorsal stream may be related to the phonological context or the connection linking input- and output phonological processes, the non-lexical route in Morton's Logogen Model, which has also been linked to the phonological loop. Alternatively in interactive models, the dorsal stream corresponds to the level of phonological segments (Dell et al., 2007). The ventral stream in turn, by corresponding to the 'semantic system' (Morton, 1980) or semantic features (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Lambon Ralph, Moriarty, & Sage, 2002), may be more involved in the interaction with the non-linguistic conceptual entities. Interestingly, within the context of distributed models of language processing (e.g., Patterson et al., 2006), the two levels of semantic features and of phonological segments have been demonstrated to interact closely both during word and

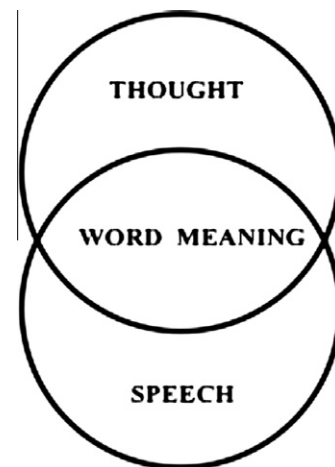


Fig. 2. The Russian psychologist Vygotski (1934) proposed "Thought" and "Speech" as overlapping psychological levels, language representing the connection between both as well as its product. "Word meaning is a phenomenon of thought only insofar as thought is embodied in speech, and of speech only insofar as speech is connected with thought and illuminated by it" (Vygotski, 1934).

non-word repetition (e.g., (Jefferies et al., 2005; Patterson et al., 1994). One may tentatively suggest that these levels of representation map onto the suggested streams.

Although some of these levels and representations may be directly related to the brain's anatomy, not all psychological and linguistic processes may be uniquely reduced to the activity of single, multiple or groups of brain regions or neural assemblies. As Freud, referring to Hughlings-Jackson (Jackson, 1879–1990) already stated, psychological theories must be regarded as a “dependent concomitant”, separately from brain localisations: “the psychological is an event parallel with the physiological” (Freud, 1891).

10. Two streams for language: a synthesis

As Wernicke more than 100 years ago speculatively yet quite rightly proposed, recent brain mapping studies suggest that it is not single brain areas or a single tract system, but the context-dependent and bidirectional interaction of anterior and posterior language zones and non-linguistic conceptual processing along two major and equivalent streams which seem to be necessary for language. A dual loop system possesses the synergy between time processing for correct serial alignment of segments by comparison with acquired (phonological) representations as a possible function of the dorsal stream and identification of an invariant set of auditory (and probably also visual) structures of elements (object, word or syntax) along the ventral stream, which makes language possible.

It is the evolution of this well interacting dual loop system, which allows the exchange of information between post- and pre-rolandic brain regions to abstract conceptual from perceptual information to express thought and to build concepts through linguistic experience. We speculate that in parallel with the development of higher-order, heteromodal brain regions (Petrides & Pandya, 2007), it is this additional potential of flexibility in the interaction within the dual system, which represents a major evolutionary advantage.

In this system of two equivalent streams, hierarchy is not determined by one specific stream, although specific functions may primarily or crucially involve one of both, but rather by an extension of this system to regulatory, cytoarchitectonically more developed

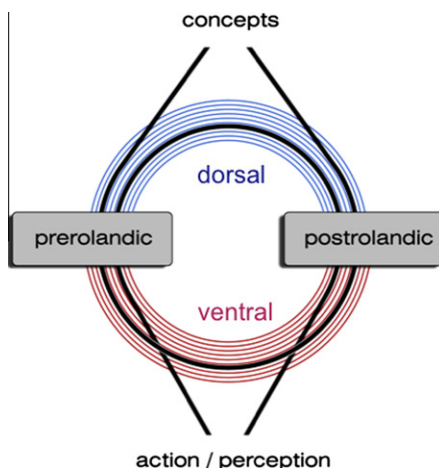


Fig. 3. A modified diagram of the ideas developed since 1874, incorporating modern brain imaging results for language processing along a dual pathway system connecting post- and prerolandic brain regions. The temporal and frontal centers connected along ventral and dorsal tracts constitute a dual loop system for processing language, bidirectionally and in parallel. This dual loop system is connected itself for top-down control with prefrontal cortices as well as with executive and primary input receiving regions. Note that dorsal and ventral tracts will differ according to the brain areas they connect, depending on the domain.

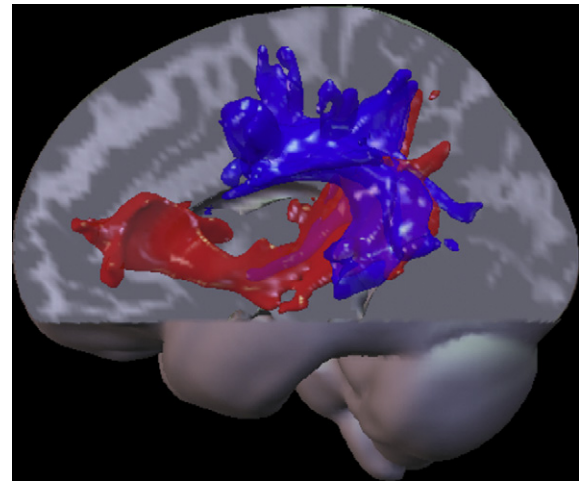


Fig. 4a. Composite diagram of the ventral (red) and dorsal (blue) DTI based trackings of several studies (Saur et al., 2008; Umarova et al., 2010; Vry et al., 2009). Tracts that connect cortical areas both ventrally and dorsally are not displayed.

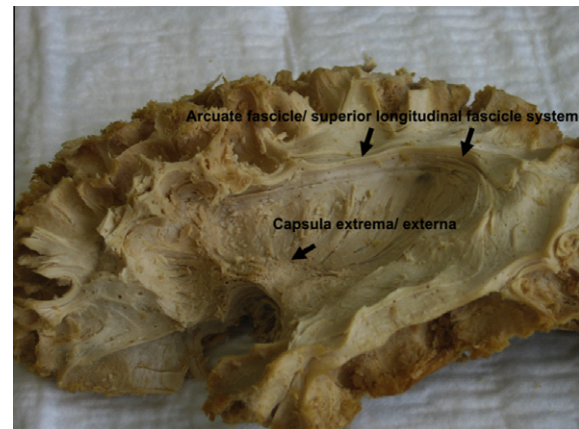


Fig. 4b. Anatomical preparation of the ventral and dorsal tracts (courtesy of Hubertus Axer, Dep. of Neurology, Jena, Germany).

areas in prefrontal, temporal and parietal neocortex in humans. (Fig. 3) The dorsal tract connects predominantly to premotor areas, such as pars opercularis of Broca's area (BA 6 and BA 44), while the ventral tract mainly connects with prefrontal regions such as pars triangularis of Broca's area (BA 45) and pars orbitalis (BA 47), a place for integration of word meaning with world knowledge (Hagoort, Hald, Bastiaansen, & Petersson, 2004), as well as frontopolar cortex (BA 9 and 10). This structure suggests an overall organization with a centrifugal gradient, centered on the primary cortices around the central sulcus or auditory cortex. This puts the dorsal stream closer to the primary brain regions, related to the environmental end of the action/perception cycle (Fuster, 2009) as used in stimulus dependent behavior of the motor repertoire (“reactive”). In contrast, the ventral stream is related more closely to “higher order” more anterior cortices for cognitive or internal behavior and abstract thinking (“reflective”) (Figs. 3 and 4). Therefore, language, for all its sophistication in humans, still seems to adhere to the basic organizational principles of the brain.

Notes

We use the term “tract” to describe fiber connections in the brain.

“Pathway”, “stream” or “route” denote cognitive processes. “Network”, “system” denote cortical regions and their connections.

We have added some phrases (in italics in parentheses) here and there to improve readability of the translated German original texts.

Acknowledgments

All cited German texts were translated by the authors. The first author has been supported by the Deutsche Forschungsgemeinschaft and the Bundesministerium für Bildung und Forschung. We thank Ralf Kramer for the drawing of Fig. 3 and our colleagues Dres. Roza Umarova, Magnus-Sebastian Vry and Volkmar Glauche for the continuing discussions and Hubertus Axer, Jena for Fig. 4b.

References

- Agosta, F., Henry, R. G., Migliaccio, R., Neuhaus, J., Miller, B. L., Dronkers, N. F., et al. (2010). Language networks in semantic dementia. *Brain*, 133(Pt 1), 286–299.
- Altmann, G., & Steedman, M. (1988). Interaction with context during human sentence processing. *Cognition*, 30(3), 191–238.
- Anwander, A., Tittgemeyer, M., von Cramon, D. Y., Friederici, A. D., & Knosche, T. R. (2007). Connectivity-based parcellation of Broca's area. *Cerebral Cortex*, 17(4), 816–825.
- Barmiou, D. E., Musiek, F. E., & Luxon, L. M. (2003). The insula (island of Reil) and its role in auditory processing: Literature review. *Brain Research Brain Research Review*, 42, 143–154.
- Barmiou, D. E., Musiek, F. E., Stow, I., Stevens, J., Cipolotti, L., Brown, M. M., et al. (2006). Auditory temporal processing deficits in patients with insular stroke. *Neurology*, 67(4), 614–619.
- Bastian, H. C. (1869). On the various forms of loss of speech in cerebral disease. *Quarterly Journal of Practical Medicine and Surgery*, 43(209–236), 470–492.
- Belin, P., & Zatorre, R. J. (2000). “What”, “where” and “how” in auditory cortex. *Nature Neuroscience*, 3(10), 965–966.
- Berke, J. J. (1960). The claustrum, the external capsule and the extreme capsule of *Macaca mulatta*. *Journal of Comparative Neurology*, 115(3), 297–331.
- Bernard, D. (1885). De l'aphasie at des ses diverses formes. *Publications du Progres medical*.
- Binder, J. (2002). Wernicke aphasia: A disorder of central language processing. In D'Eposito (Ed.), *Neurological foundations of cognitive neuroscience* (pp. 175–238). MIT Press.
- Bookheimer, S. (2002). Functional MRI of Language: New approaches to understanding the cortical organization of semantic processing. *Annual Review of Neuroscience*, 25, 151–188.
- Bornkessel, I., Zysset, S., Friederici, A. D., von Cramon, D. Y., & Schlesewsky, M. (2005). Who did what to whom? The neural basis of argument hierarchies during language comprehension. *NeuroImage*, 26(1), 221–233.
- Bucy, P. C., & Klüver, H. (1955). An anatomical investigation of the temporal lobe in the monkey (*Macaca mulatta*). *Journal of Comparative Neurology*, 103, 151–252.
- Burdach, K. F. (1826). *Vom Baue und Leben des Gehirns*. Leipzig: Dyk'sche Buchhandlung.
- Caplan, D., Vijayan, S., Kuperberg, G., West, C., Waters, G., Greve, D., et al. (2002). Vascular responses to syntactic processing: Event-related fMRI study of relative clauses. *Human Brain Mapping*, 15(1), 26–38.
- Catani, M., Howard, R. J., Pajevic, S., & Jones, D. K. (2002). Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *NeuroImage*, 17, 77–94.
- Catani, M., Jones, D. K., & ffytche, D. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, 57, 8–16.
- Catani, M., & Mesulam, M. M. (2008). The arcuate fascicle and the disconnection theme in language and aphasia: History and current state. *Cortex*, 44, 953–961.
- Corbett, F., Jefferies, E., Ehsan, S., & Lambon Ralph, M. A. (2009). Different impairments of semantic cognition in semantic dementia and semantic aphasia: Evidence from the non-verbal domain. *Brain*, 132, 2593–2608.
- Crick, F., & Koch, C. (2005). What is the function of the claustrum? *Philosophical Transactions of the Royal Society London*, 360, 1271–1279.
- Croxson, P. L., Johansen-Berg, H., Behrens, T. E., Robson, M. D., Pinski, M. A., Gross, C. G., et al. (2005). Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *Journal of Neuroscience*, 25(39), 8854–8866.
- De Bleser, R., Cubelli, R., & Luzzatti, C. (1993). Conduction aphasia, misrepresentations and word representations. *Brain and Language*, 45, 475–494.
- Dell, G. S., Martin, N., & Schwartz, M. F. (2007). A case-series test of the interactive two-step model of lexical access: Predicting word repetition from picture naming. *Journal of Memory and Language*, 2007(56), 490–520.
- Dell, G. S., Schwartz, M. F., Martin, N., Saffran, E. M., & Gagnon, D. A. (1997). Lexical access in aphasic and nonaphasic speakers. *Psychological Review*, 104(4), 801–838.
- Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature*, 384(14), 159–161.
- Duffau, H. (2008). The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. *Neuropsychologia*, 46, 927–934.
- Duffau, H., Gatignol, P., Moritz-Gasser, S., & Mandonnet, E. (2009). Is the left uncinate fascicle essential for language? A cerebral stimulation study. *Journal of Neurology*, 256, 382–389.
- Edelstein, L. R., & Denaro, F. J. (2004). The claustrum: A historical review of its anatomy, physiology, cytochemistry and functional significance. *Cellular and Molecular Biology*, 50(6), 675–702.
- Fiebach, C. J., Schlesewsky, M., Lohmann, G., von Cramon, D. Y., & Friederici, A. D. (2005). Revisiting the role of Broca's area in sentence processing: Syntactic integration versus syntactic working memory. *Human Brain Mapping*, 24(2), 79–91.
- Forkstam, C., & Petersson, K. M. (2005). Towards an explicit account of implicit learning. *Current Opinion in Neurology*, 18(4), 435–441.
- Frazier, L. (1987). Sentence processing: A tutorial review. In M. Coltheart (Ed.), *Attention and performance XII: The psychology of reading* (pp. 559–586). London: Lawrence Erlbaum.
- Freud, S. (1891). *Zur Auffassung der Aphasien. Eine kritische Studie* (2nd ed.). Leipzig and Wien: Franz Deuticke.
- Frey, S., Campbell, J. S. W., Pike, G. B., & Petrides, M. (2008). Dissociating the human language pathway with high angular resolution diffusion fiber tractography. *Journal of Neuroscience*, 28(5), 11435–11444.
- Friederici, A. D. (2009). Pathways to language: Fibre tracts in the human brain. *Trends in Cognitive Sciences*, 13(4), 175–181.
- Friederici, A. D., Bahlmann, J., Heim, S., Schubotz, R. I., & Anwander, A. (2006). The brain differentiates human and non-human grammars: Functional localization and structural connectivity. *Proceedings of the National Academy of Sciences USA*, 103, 2458–2463.
- Friederici, A. D., Pannekamp, A., Partsch, C. J., Ulmen, U., Oehler, K., Schmutzler, R., et al. (2008). Sex hormone testosterone affects language organization in the infant brain. *NeuroReport*, 19(3), 283–286.
- Friedrich, R., & Friederici, A. D. (2009). Mathematical logic in the human brain: Syntax. *Plos One*, 4(5), e5599.
- Fuster, J. (2009). Cortex and memory: Emergence of a new paradigm. *Journal of Cognitive Neuroscience*, 21(11), 2047–2072.
- Geschwind, N. (1965). Disconnection syndromes in animals and man. *Brain*, 88(237–294), 585–644.
- Geschwind, N. (1967). Wernickes contribution to the study of aphasia. *Cortex*, 3, 449–463.
- Geschwind, N. (1972). Language and the brain. *Scientific American*, 226, 76–83.
- Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex*, 18(11), 2471–2482.
- Gloor, P. (1997). *The temporal lobe and limbic system*. New York: Oxford University Press.
- Goldstein, K. (1927). *Die Lokalisation in der Großhirnrinde nach den Erfahrungen am kranken Menschen*. Berlin: Springer.
- Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., et al. (2004). What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain*, 127, 628–649.
- Hagoort, P. (2005). On Broca, brain, and binding: A new framework. *Trends in Cognitive Sciences*, 9(9), 416–423.
- Hagoort, P., Hald, L., Bastiaansen, M., & Petersson, K. M. (2004). Integration of word meaning and world knowledge in language comprehension. *Science*, 304, 438–441.
- Hanley, J. R., Dell, G. S., Kay, J., & Baron, R. (2004). Evidence for the involvement of a nonlexical route in the repetition of familiar words: A comparison of single and dual route models of auditory repetition. *Cognitive Neuropsychology*, 21, 147–158.
- Head, H. (1926). *Aphasia and kindred disorders of speech*. New York: Macmillan.
- Heilbrunner, K. (1908). Zur Symptomatologie der Aphasie mit besonderer Berücksichtigung zwischen Sprachverständnis, Nachsprechen und Wortfindung. *Archiv für Psychiatrie und Zeitschrift Neurologie*, 43, 234–298.
- Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition*, 92, 67–99.
- Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, 8, 393–402.
- Hodges, J. R., Patterson, K., Oxbury, S., & Funnel, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain*, 115, 1783–1806.
- Houde, J. F., & Jordan, M. I. (1998). Sensorimotor adaptation in speech production. *Science*, 279(5354), 1213–1216.
- Jackendoff, R. (1997). *The architecture of the language faculty*. Cambridge: The MIT Press.
- Jackendoff, R. (2009). Parallels and nonparallels between language and music. *Music Perception*, 26(3), 195–204.
- Jackson, J. H. (1879–90). On affections of speech from disease of the brain. *Brain*, 2, 220–222, 323–356.
- Jefferies, E., Bateman, D., & Lambon Ralph, M. A. (2005). The role of the temporal lobe semantic system in number knowledge: Evidence from late stage semantic dementia. *Neuropsychologia*, 43(6), 887–905.
- Jefferies, E., & Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: A case series comparison. *Brain*, 129, 2132–2147.
- Kaas, J. H., & Hackett, T. A. (1999). “What” and “where” processing in auditory cortex. *Nature Neuroscience*, 2, 1045–1047.

- Kleist, K. (1905). Über Leitungsaplasie. *Monatsschrift für Psychiatrie und Neurologie*, 17, 503–532.
- Kleist, K. (1934). *Gehirmpathologie*. Leipzig: Barth.
- Kohn, S. E. (1992). *Conduction aphasia*. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Kraepelin, E. (1901). *Einführung in die Psychiatrische Klinik*. Leipzig: Barth.
- Lambon Ralph, M. A. (1998). Distributed versus localist representations: Evidence from the study of item consistency in a case of classical anomia. *Brain and Language*, 64, 339–360.
- Lambon Ralph, M. A., Moriarty, L., & Sage, K. (2002). Anomia is simply a reflection of semantic and phonological impairments: Evidence from a case-series study. *Aphasiology*, 16, 56–82.
- Lambon Ralph, M. A., & Patterson, K. (2008). Generalisation and differentiation in semantic memory: Insights from semantic dementia. *Annals of the New York Academy of Sciences*, 1124, 61–76.
- Lambon Ralph, M. A., Sage, K., & Roberts, J. (2000). Classical anomia: A neuropsychological perspective on speech production. *Neuropsychologia*, 38, 186–202.
- Lecours, A. R., Chain, F., Poncet, M., & Nespoulos, J. L. (1992). Paris 1908: The hot summer of aphasiology or a season in the life of a chair. *Brain and Language*, 42, 105–152.
- Levelt, W. J. (1999). Models of word production. *Trends in Cognitive Sciences*, 3(6), 223–232.
- Lieberman, A. M., Cooper, F. S., Shankweiler, D., & Studdert-Kennedy, M. (1967). Perception of the speech code. *Psychological Review*, 74, 431–461.
- Lieberman, A. M., & Mattingly, I. G. (1985). The motor theory of speech perception revised. *Cognition*, 21, 1–36.
- Lichtheim, L. (1885). On aphasia. *Brain*, 7, 433–484.
- Lu, J. H., Crosson, B., Nadeau, S. E., Heilman, K., Gonzales-Rothi, L. J., Raymer, A., et al. (2002). Category-specific naming deficits for objects and actions: Semantic attribute and grammatical role hypotheses. *Neuropsychologia*, 40(9), 1608–1621.
- Ludwig, E., & Klingler, J. (1956). *Atlas Cerebri Humani*. Basel, New York: Karger.
- MacDonald, M. C., Pearlmuter, N. J., & Seidenberg, M. S. (1994). The lexical nature of syntactic ambiguity resolution [corrected]. *Psychological Review*, 101(4), 676–703.
- Makris, N., Meyer, J. W., Bates, J. F., Yeterian, E. H., Kenney, D. N., & Caviness, V. S. (1999). MRI-Based topographic parcellation of human cerebral white matter and nuclei. II. Rationale and applications with systematics of cerebral connectivity. *NeuroImage*, 9, 18–45.
- Makris, N., & Pandya, D. (2009). The extreme capsule in humans and rethinking of the language circuitry. *Brain Structure Function*, 213(3), 343–358.
- Makuuchi, M., Bahlmann, J., Anwander, A., & Friederici, A. D. (2009). Segregating the core computational faculty of human language from working memory. *Proceedings of the National Academy of Sciences USA*, 106(20), 8362–8367.
- Marslen-Wilson, W., & Tyler, L. K. (1980). The temporal structure of spoken language understanding. *Cognition*, 8(1), 1–71.
- Mathur, B. N., Caprioli, R. M., & Deutch, A. Y. (2009). Proteomic analysis illuminates a novel structural definition of the claustrum and insula. *Cerebral Cortex*, 19(10), 2372–2379.
- Matsuo, K., Mizuno, T., Yamada, K., Akazawa, K., Kasai, T., Kondo, M., et al. (2008). Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. *Neuroradiology*, 50, 605–611.
- McCarthy, R., & Warrington, E. K. (1990). Auditory-verbal span of apprehension: A phenomenon in search of a function? In T. Shallice & G. Vallar (Eds.), *Neuropsychological impairments of short-term memory* (1990/02/15 ed., pp. 176–186). Cambridge, UK: Cambridge University Press.
- Meynert, T. (1866). Ein Fall von Sprachstörung, anatomisch begründet. In C. Braun, A. Duchek, & L. Schlager (Eds.), *XII. Band der Zeitschrift der K.u.k. Gesellschaft der Ärzte in Wien* (Vol. 22, pp. 152–189). Wien.
- Mishkin, M., Ungerleider, L., & Macko, K. A. (1983). Object vision and spatial vision: Two visual pathways. *Trends in Neuroscience*, 6, 414–417.
- Moro, A., Tettamanti, M., Perani, D., Donati, C., Cappa, S. F., & Fazio, F. (2001). Syntax and the brain: Disentangling grammar by selective anomalies. *NeuroImage*, 13(1), 110–118.
- Morton, J. (1980). The logogen model and orthographic structure. In U. Frith (Ed.), *Cognitive processes in spelling* (pp. 117–133). London: Academic Press.
- Musso, M., Moro, A., Glauche, V., Rijntjes, M., Reichenbach, J., Buchel, C., et al. (2003). Broca's area and the language instinct. *Nature Neuroscience*, 6(7), 774–781.
- Obleser, J., Wise, R. J., Alex Dresner, M., & Scott, S. K. (2007). Functional integration across brain regions improves speech perception under adverse listening conditions. *Journal of Neuroscience*, 27(9), 2283–2289.
- Parker, G. J., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A., Ciccarelli, O., & Lambon-Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage*, 24(3), 656–666.
- Patel, A. D. (2007). *Music, Language, and the Brain*. New York: Oxford University Press.
- Patterson, K., Graham, H., & Hodges, J. R. (1994). The impact of semantic memory loss on phonological representations. *Journal of Cognitive Neuroscience*, 6, 57–69.
- Patterson, K., Lambon Ralph, M. A., Jefferies, E., Woolams, A., Jones, R., Hodges, J. R., et al. (2006). "Presemantic" cognition in semantic dementia: Six deficits in search of an explanation. *Journal of Cognitive Neuroscience*, 18, 169–183.
- Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, 8, 976–987.
- Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural correlates of the verbal component of working memory. *Nature*, 362, 342–344.
- Pershing, H. T. (1900). Wernicke's conduction-aphasia. *Journal of Neurological and Mental Diseases*, 27, 369–374.
- Petrides, M., & Pandya, D. N. (1988). Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *Journal of Comparative Neurology*, 273(1), 52–66.
- Petrides, M., & Pandya, D. N. (2007). Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. *Journal of Neuroscience*, 27(43), 11573–11586.
- Petrides, M., & Pandya, D. (2009). Distinct parietal and temporal pathways to the homologues of Broca's area in the monkey. *Plos Biology*, 7(8), e1000170.
- Powell, H. W., Parker, G. J., Alexander, D. C., Symms, M. R., Boulby, P. A., Wheeler-Kingshott, C. A., et al. (2006). Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study. *NeuroImage*, 32(1), 388–399.
- Rauschecker, J. (1995). Compensatory plasticity and sensory substitution in the cerebral cortex. *Trends in Neuroscience*, 18, 36–42.
- Rauschecker, J. (1998). Cortical processing of complex sounds. *Current Opinion Neurobiology*, 8, 516–521.
- Rauschecker, J. P., & Scott, S. K. (2009). Maps and strams in the auditory cortex: Nonhuman primates illuminate human speech processing. *Nature Neuroscience*, 12(6), 718–724.
- Reil, J. C. (1809). Die sylvische Grube oder das Thal, das gestreifte grosse Hirnganglion, dessen Kapsel und die Seitentheile des grossen Gehirns. *Archiv für Physiologie. Halle, Curtsche Buchhandlung* (9), 195–208.
- Rilling, J. K., Glasser, M. F., Preuss, T. M., Ma, X., Zhao, T., Hu, X., et al. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nature Neuroscience*, 11(4), 426–428.
- Ross, E. D. (2010). Cerebral localization of functions and the neurology of language: Fact versus fiction or is it something else? *Neuroscientist*, 16(3), 222–243.
- Salmelin, R., Hari, R., Lounasmaa, O., & Sams, M. (1994). Dynamics of brain activation during picture naming. *Nature*, 368, 463–465.
- Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M. S., et al. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Science USA*, 105(46), 18035–18040.
- Schmahmann, J. D., & Pandya, D. (2006). *Fiber pathways of the brain*. Oxford: Oxford University Press.
- Schmidt, J. B. (1871). Casuistik. Gehör- und Sprachstörung in Folge von Apoplexie. *Allgemeine Zeitschrift für Psychiatrie*, 27, 304–306.
- Scott, S. K., Blank, C. C., Rosen, S., & Wise, R. J. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain*, 123(Pt. 12), 2400–2406.
- Scott, S. K., & Johnsrude, I. S. (2003). The neuroanatomical and functional organization of speech perception. *Trends in Neuroscience*, 26, 100–107.
- Seltzer, B., & Pandya, D. N. (1984). Further observations on parieto-temporal connections in the rhesus monkey. *Experimental Brain Research*, 55(2), 301–312.
- Sharp, D. J., Awad, M., Warren, J. E., Wise, R. J., Vigliocco, G., & Scott, S. K. (2010). The neural response to changing semantic and perceptual complexity during language processing. *Human Brain Mapping*, 31(3), 365–377.
- Stromswold, K., Caplan, D., Alpert, N., & Rauch, S. (1996). Localization of syntactic comprehension by positron emission tomography. *Brain and Language*, 52(3), 452–473.
- Tettamanti, M., Alkadhi, H., Moro, A., Perani, D., Kollias, S., & Weniger, D. (2002). Neural correlates for the acquisition of natural language syntax. *NeuroImage*, 17, 700–709.
- Tettamanti, M., & Weniger, D. (2006). Broca's area: A supramodal hierarchical processor? *Cortex*, 42(4), 491–494.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Science USA*, 94(26), 14792–14797.
- Trolard, P. (1906). Le Faisceau longitudinal inférieur du cerveau. *Revue Neurologique*, 14, 440–446.
- Umarova, R., Saur, D., Schnell, S., Kaller, C., Vry, M. S., Glauche, V., et al. (2010). Structural connectivity for visuospatial attention: Significance of ventral pathways. *Cerebral Cortex*, 20(1), 121–129.
- Vallar, G., Di Betta, A. M., & Silveri, M. C. (1997). The phonological short-term store-rehearsal system: Patterns of impairment and neural correlates. *Neuropsychologia*, 35, 795–912.
- Vigneau, M., Beaucois, V., Herve, P. Y., Duffau, H., Crivello, F., Houde, O., et al. (2006). Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. *NeuroImage*, 30, 1414–1432.
- von Monakow, C. (1885). Neue experimentelle Beiträge zur Anatomie der Schleife: vorläufige Mitteilung. *Neurologisches Centralblatt*, 12, 265–268.
- Vry, M. S., Saur, D., Umarova, R., Kreher, B. W., Schnell, S., Glauche, V., et al. (2009). Functionally guided DTI-based probabilistic fiber pathway extraction shows distinct connection profiles for parieto-premotor and parieto-prefrontal cortical networks in the context of motor imagery and execution. *NeuroImage*, 47(suppl. 1), S172.
- Vygotski, L. S. (1934). *Thought and language*. Cambridge: MIT Press.
- Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta analysis. *Cognitive, Affective & Behavioural Neuroscience*, 3, 255–274.
- Warren, J. E., Crinion, J., Lambon Ralph, M. A., & Wise, R. J. S. (2009). Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. *Brain*, 132, 3428–3442.
- Weiller, C., Musso, M., Rijntjes, M., & Saur, D. (2009). Please don't underestimate the ventral pathway in language. *Trends in Cognitive Science*, 13(9), 369–370.
- Wernicke, C. (1874). *Der aphasische Symptomenkomplex. Eine psychologische Studie auf Anatomischer Basis*. Breslau: Cohn und Weigert.

- Wernicke, C. (1886). Die neueren Arbeiten über Aphasie. *Fortschritte der Medizin*, 4, 371–377.
- Wernicke, C. (1903). The symptom complex of aphasia. *Monatsschrift für Psychiatrie und Neurologie*(4), 265–324.
- Wernicke, C. (1906). Der aphasische Symptomenkomplex. In E. v. Leyden (Ed.), *Deutsche Klinik am Eingang des zwanzigsten Jahrhunderts in akademischen Vorlesungen* (Vol. VI, pp. 487–556). Berlin: Urban & Schwarzenberg.
- Wernicke, C. (1908). The symptom complex of aphasia. In E. Church (Ed.), *Diseases of the nervous system*. New York & London.
- Wise, R. J. S. (2003). Language systems in normal and aphasic subjects: Functional imaging studies and inferences from animal studies. *British Medical Bulletin*, 65, 95–119.